Role of TGF-β signaling pathway variants in cancer development and progression

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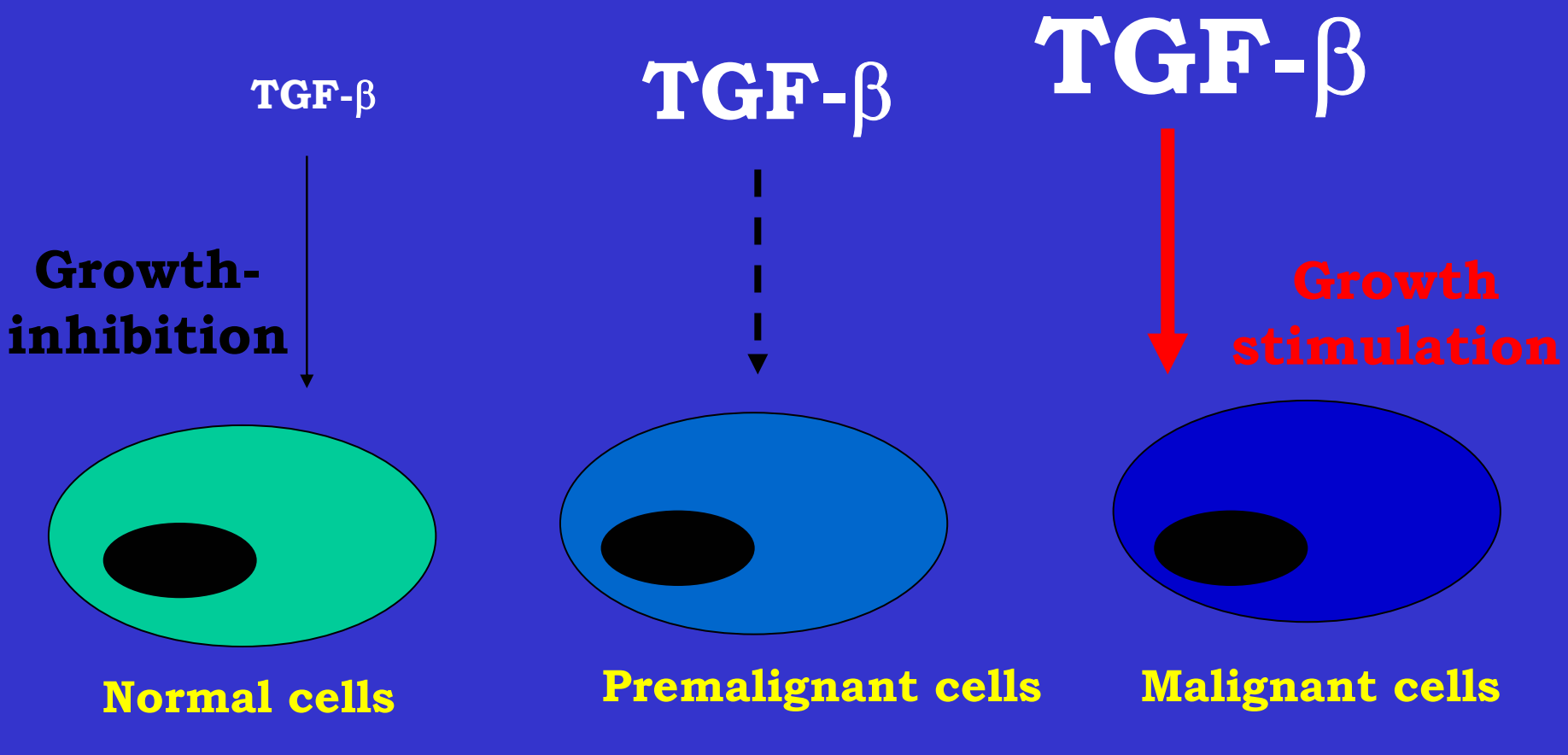
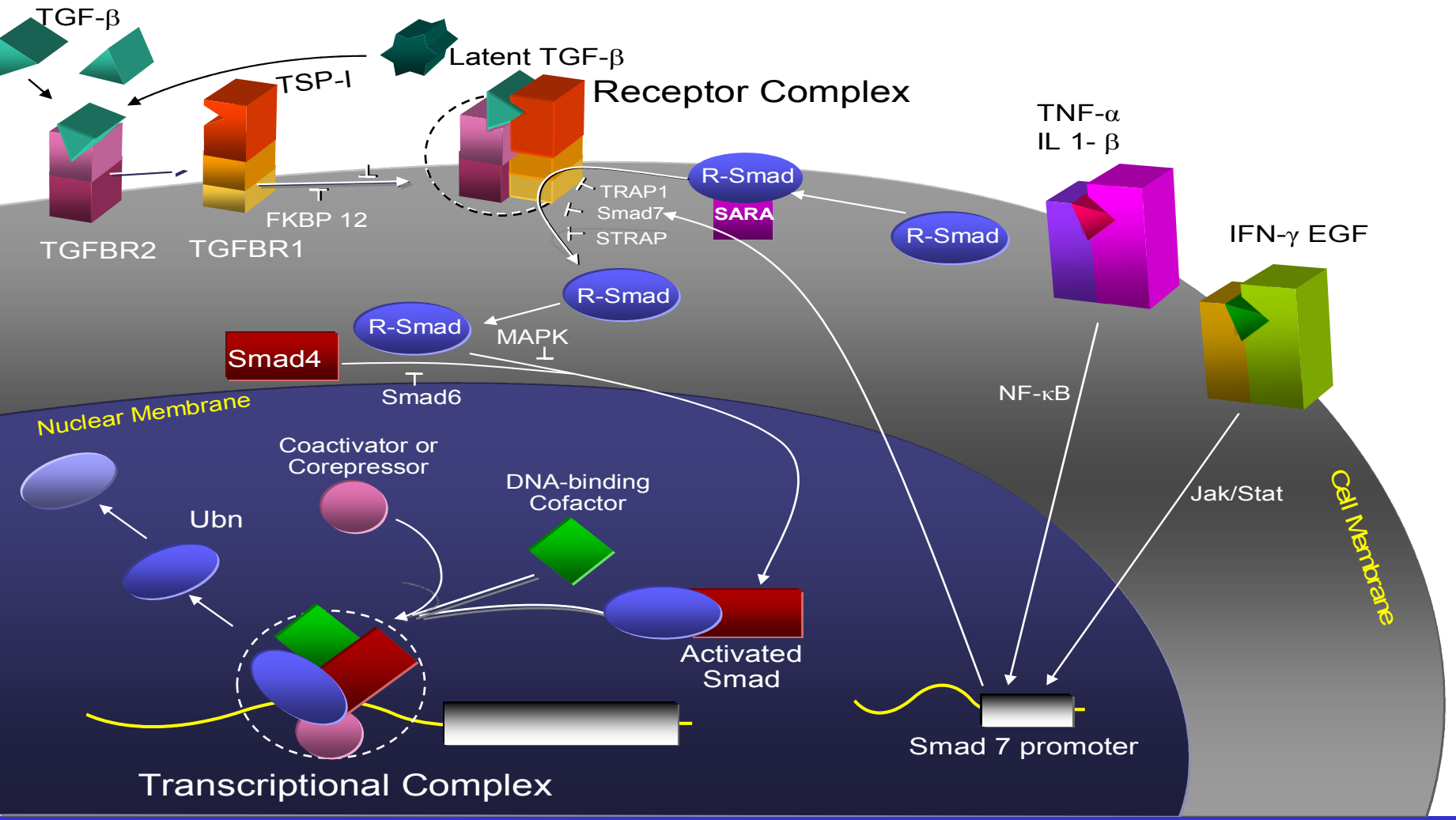
Analyses of cohorts of twins show a relatively large effect of heritability for several forms of cancer suggesting that our current knowledge of the genetics of cancer is limited.

This effect is likely due to a combination of low-penetrance tumor susceptibility genes. Such variants are relatively common in the population and as such may confer a much higher attributable risk in the general population than rare mutations in high-penetrance cancer susceptibility genes.

Candidate low-penetrance genes are chosen on the basis of biological plausibility. Alterations in their protein sequence, and therefore function, could affect pathways involved in cell growth control, detoxification and carcinogenesis.

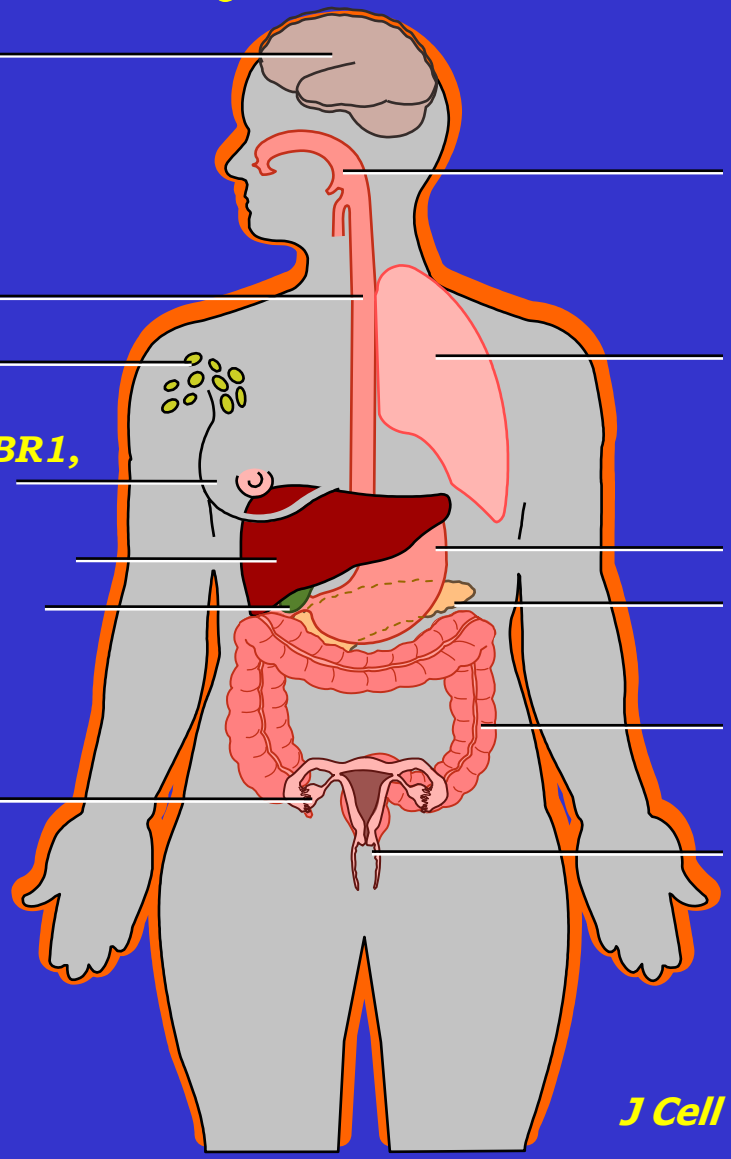
Transforming Growth Factor Beta (TGF-β) is a potent inhibitor of normal epithelial cell growth. However, in the presence of TGF-β cancer cells are only partially growth-inhibited by TGF- β. Some cancer cells are even growth-stimulated by TGF- β. The TGF- β signaling pathway has emerged as a major cancer-related pathway.





Transforming growth factor beta pathway and its interaction with other common growth factor pathways (*Expert Rev Anticancer Ther* 2004, 4:649-61)

TGF-β pathway alterations in cancer



TGFBR2

TGFBR2

TGFBR1, TGFBR2

↓TGFBR2, ↓SMAD4; *TGFBR1, TGFBR2, SMAD4* del

TGFBR1, SMAD2, SMAD4

TGFBR1, TGFBR2, SMAD4

↓TGFBR2, *TGFBR2*

↓TGFBR2; *TGFBR2, SMAD4*

↓TGFBR2; *SMAD2, SMAD4*

↓TGFBR1; *TGFBR2*

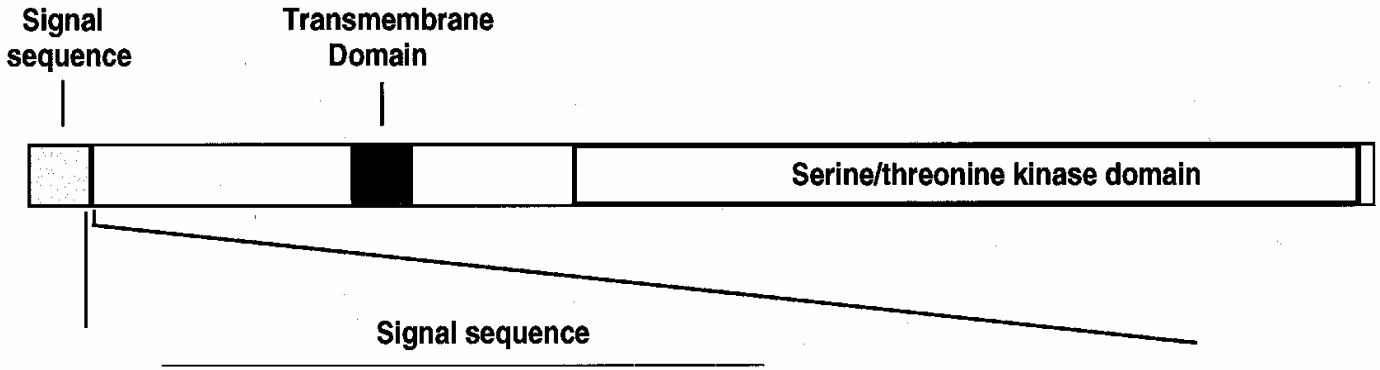
TGFBR1, SMAD4 del; ↑SMAD2, ↑SMAD7

TGFBR2, SMAD2, SMAD4

TGFBR2

J Cell Phys 2001, 186:153-168

TGFBR1 and its mutant alleles



14 ...Leu Val Leu Ala Ala Ala Ala Ala Ala Ala Ala Ala Leu Leu Pro... 30 *TβR-I*

42 ...CTC GTG CTG GCG GCG GCG GCG GCG GCG GCG GCG GCG CTG CTC CCG... 119

14 ...Leu Val Leu Ala Ala Ala Ala Ala Ala Leu Leu Pro... 27 *TβR-I(6A)*

42 ...CTC GTG CTG GCG GCG GCG GCG GCG GCG CTG CTC CCG... 110

14 ...Leu Val Leu Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Leu Leu Pro... 31 *TβR-I(10A)*

42 ...CTC GTG CTG GCG GCG GCG GCG GCG GCG GCG GCG GCG CTG CTC CCG... 122

Cancer Res 58:2727-2732, 1998

TGFBR1 genotypes in cases and controls from New York City

total	*TGFBR1/ TGFBR1*	*TGFBR1/ TGFBR1*6A*	*TGFBR1*6A/ TGFBR1*6A*	*TGFBR1/ TGFBR1*8A*	*TGFBR1/ TGFBR1*5A*	*TGFBR1/ TGFBR1*10A*	*TGFBR1*6A TGFBR1*10A*
Controls							
735	**654**	**78 (10.6 %)**	**0**	**2**	**1**	**0**	**0**
Cases							
851	**716**	**123 (14.5 %)**	**9(1.1 %)**	**0**	**0**	**2**	**1**

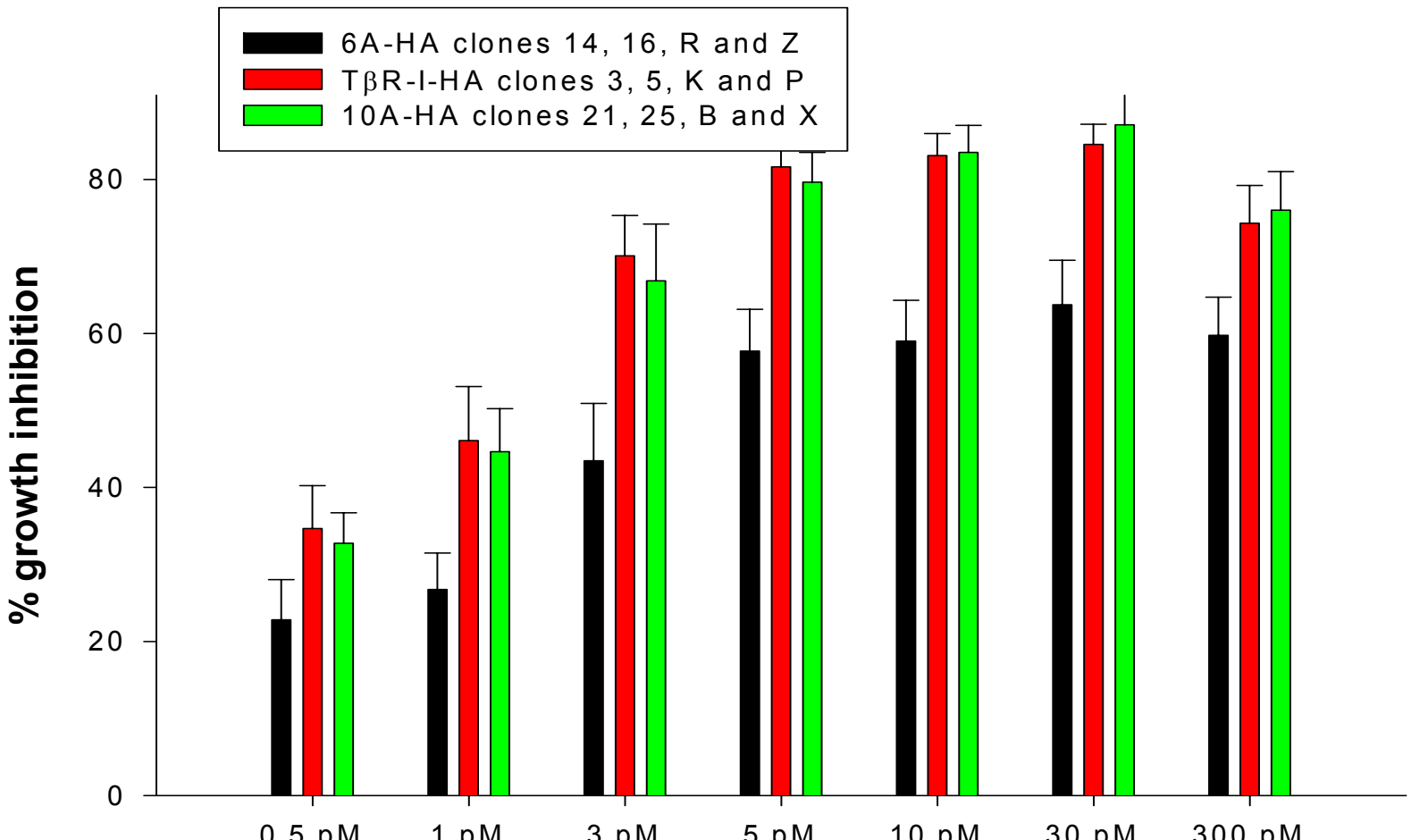
($p < 0.02$, Fischer's exact test) **($p < 0.01$, Fischer's exact test)**

***Cancer Res* 59:5678-5682, 1999**

TGFBR1 genotypes in cancer cases from New York City

	total	*TGFBR1/ TGFBR1*	*TGFBR1/ TGFBR1*6A*	*TGFBR1*6A/ TGFBR1*6A*	*TGFBR1/ TGFBR1*10A*	*TGFBR1*6A/ TGFBR1*10A*
Colon Cancer n=112	**90**	**17 (15%)**	**4**	**-**	**1**
Ovarian Cancer n=48	**39**	**7 (13%)**	**1**	**1**	**-**
Breast Cancer n=152	**128**	**24 (16%)**	**-**	**-**	**-**
Non-Hodgkin Lymphoma n=80	**66**	**13 (16%)**	**1**	**-**	**-**
Germ Cell Cancer n=57	**50**	**5 (9%)**	**2**	**-**	**-**
Non-Small Cell Lung Cancer n=93	**81**	**11 (12%)**	**1**	**-**	**-**
Prostate Cancer n=59	**51**	**8 (14%)**	**-**	**-**	**-**

***Cancer Res* 59:5678-5682, 1999**



Pasche et al., *Cancer Res* 59:5678-5682, 1999

All Cancers: *6A/*9A or *6A/*6A

Citation	Cases	Controls
Pasche US 1999	141 / 1702	78 / 1470
Tilborg 2001	25 / 292	38 / 366
Baxter 2002	165 / 1318	43 / 496
Chen 1999	12 / 132	7 / 136
Samowitz 2001	50 / 504	68 / 724
Pasche Italy 1999	53 / 694	12 / 100
Stefanovska_letter 2001	10 / 234	22 / 400
Overall (7)	456 / 4876	268 / 3692

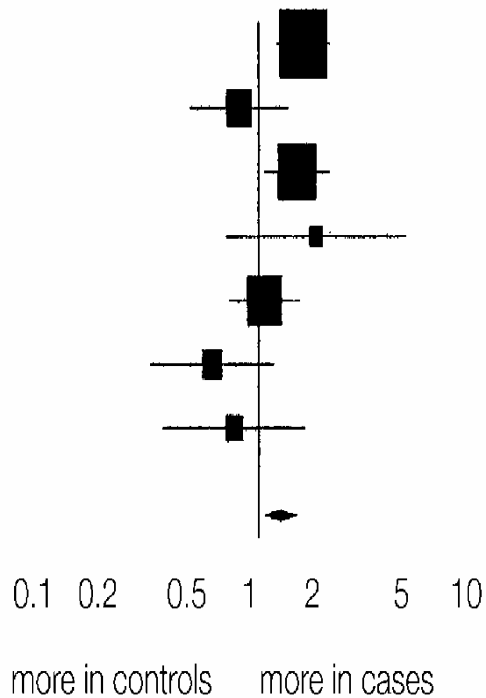
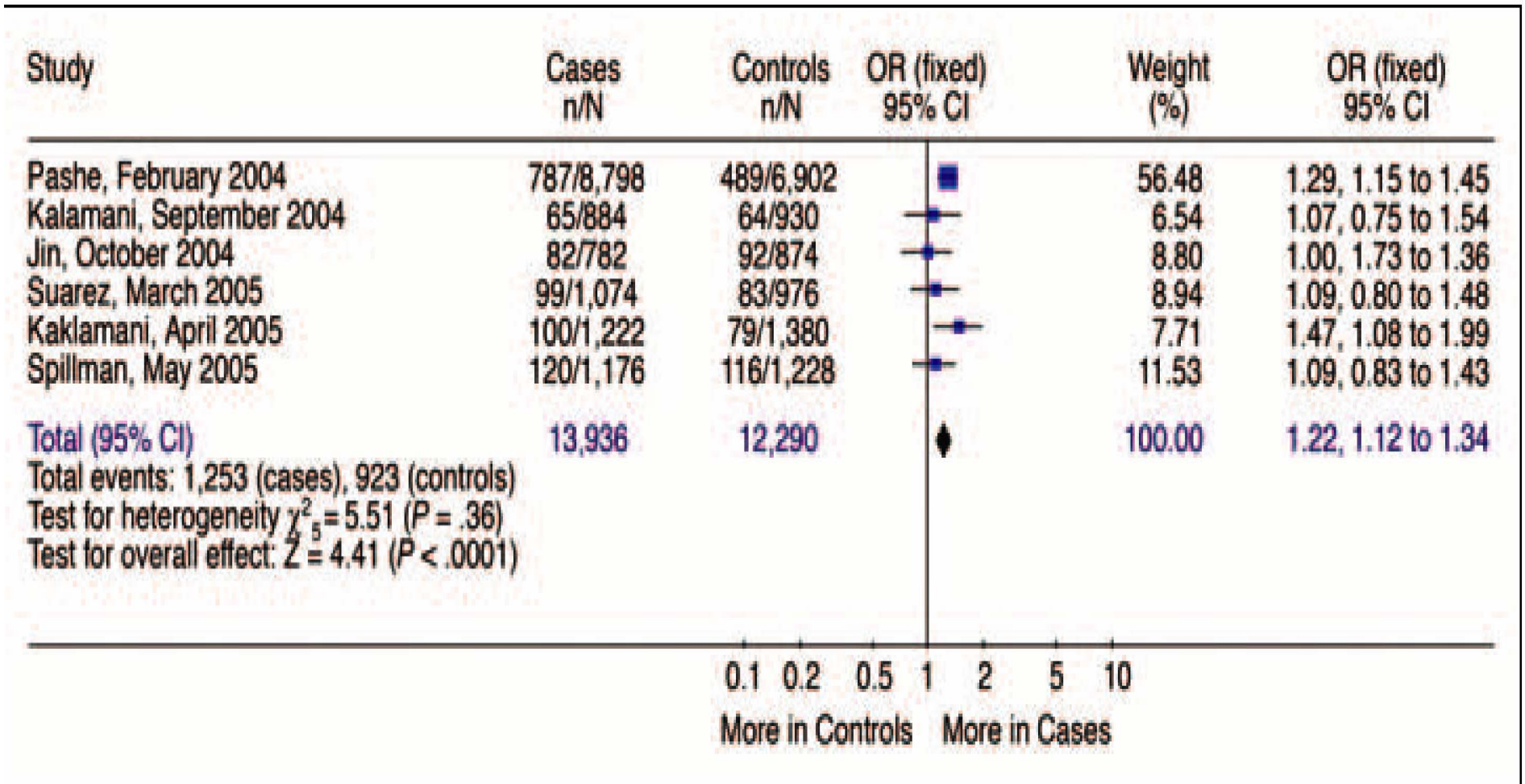


Fig 1. Meta-analysis of *6A for all cancers. The numbers under "Cases" and "Controls" represent *6A alleles out of all alleles.

Kaklamani et al, *Journal of Clinical Oncology* 2003, 21:3236-3243

*TGFBR1**6A and cancer risk: meta-analysis of 17 studies



Zhang et al, *Journal of Clinical Oncology* 2005, 23:7743-7744

Table 3. ORs and 95% CIs According to cTumor Type

	No. of Cases		No. of Controls		All Cancers		Breast Cancer		Colon Cancer		Ovarian Cancer	
	No.	%	No.	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Total No. of Subjects	4,399		3,451		—	—	1,420		1,585		409	
*9A/*9A	3640	82.7	2975	86.2	—	—	—	—	—	—	—	—
*9A/*6A	717	16.3	457	13.2	1.19†	1.06, 1.36	1.34†	1.10, 1.63	1.14	.95, 1.36	1.29	.92, 1.81
*6A/*6A	35	0.8	16	0.5	1.70*	1.11, 2.59	2.13	.98, 4.62	2.02*	1.18, 3.48	2.69*	1.08, 6.71
*9A/*6A or *6A/*6A	752	17.1	489	14.1	1.24†	1.10, 1.40	1.38†	1.14, 1.67	1.20*	1.01, 1.43	1.41*	1.02, 1.95

Abbreviation: OR, odds ratio.
*$P = .05 \geq P > .01$
†$P \leq .01$

***J Clin Onc* 2004, 22:756-758**

Table 1. Odds Ratios and 95% CIs According to Tumor Type

	Breast Cancer		Prostate Cancer		Ovarian Cancer	
	OR	95% CI	OR	95% CI	OR	95% CI
Total No. of cases	2,422		1,038		997	
Total No. of controls	2,998		1,688		1,720	
9A/9A	1.00		1.00		1.00	
9A/6A	1.23†	1.06 to 1.43	1.02	0.81 to 1.29	1.11	0.89 to 1.39
6A/6A	2.69†	1.54 to 4.68	3.00	1.21 to 7.44	2.07	1.18 to 3.64
9A/6A or 6A/6A	1.31†	1.13 to 1.51	1.10	0.88 to 1.38	1.21	0.99 to 1.49

Abbreviation: OR, odds ratio.
.01 *P* .05.
†*P* .01.

Pasche et al., *J Clin Onc* 2005, 23:7744-7746, 2005

INCREASED TGF-β SIGNALING AND BREAST CANCER

Transgenic animal experiments suggest that increased expression of TGF-β1 (TGFB1) is protective against breast cancer development.

A T→C (thymine to cytosine) transition in the 29th nucleotide of *TGFB1* coding sequence results in a leucine to proline substitution at the 10th amino acid and is associated with increased serum levels of TGFB1.

A study of 3,075 postmenopausal Caucasian females shows that the *TGFB1CC is associated with a significant decreased risk of breast cancer: hazard ratio (HR), 0.36; 95% confidence interval (CI), 0.17-0.75 (Ziv et al., 2001).**

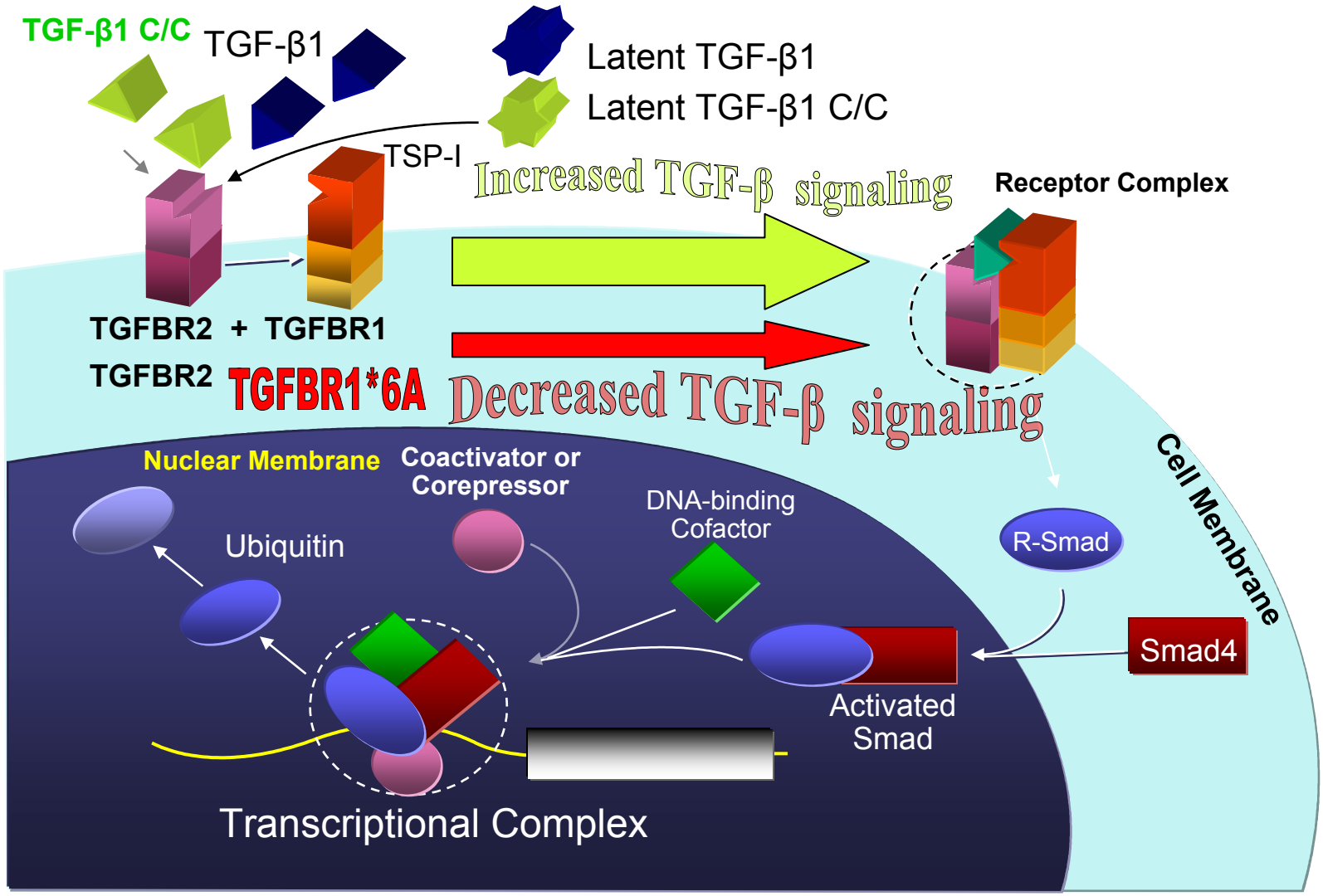
Ziv et al., *JAMA* 2001, 285:2859-2863

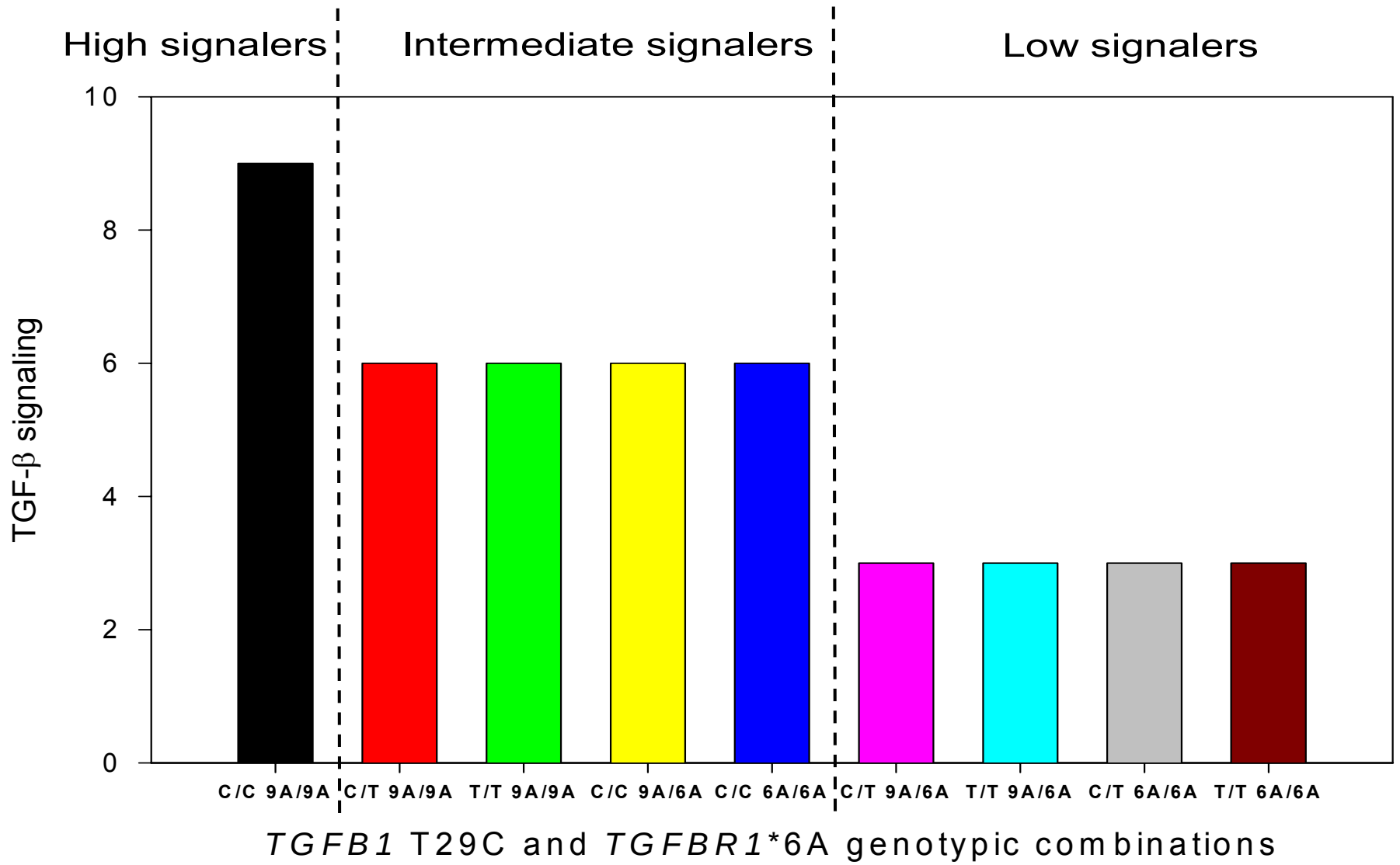
INCREASED TGF-β SIGNALING AND BREAST CANCER

More recent investigations of this polymorphism with regard to breast cancer risk have yielded conflicting results. In a pooled analysis of three European case-control studies that included 3,987 cases and 3,867 controls with a median age of 50, the *TGFB1CC genotype was associated with a 21% increased risk of breast cancer.**

In a hospital-based study of 232 cases and 172 controls conducted in Japan, there was no overall association between the *TGFB1CC genotype and breast cancer. However, for premenopausal women, the *TGFB1**CC genotype was significantly associated with reduced risk of breast cancer in comparison with the *TGFB1**TT genotype (OR=0.45, 0.20-0.98).**

Dunning et al., *Cancer Res* 2003, 63:2610-2615
Hishida et al., *Breast Cancer* 2003, 10:63-69


TGF-β1 C/C
TGF-β1
Latent TGF-β1
Latent TGF-β1 C/C
TSP-I
Increased TGF-β signaling
Receptor Complex
TGFBR2 + TGFBR1
TGFBR2
TGFBR1*6A
Decreased TGF-β signaling
Nuclear Membrane
Coactivator or Corepressor
DNA-binding Cofactor
Ubiquitin
R-Smad
Cell Membrane
Smad4
Activated Smad
Transcriptional Complex



Kaklamani et al., *Cancer Res* 2005, 65:3454-3461

Table 1. Study population

	TGFBR1 study population*			*TGFB1* study population†		
	Cases (n = 611), n (%)	Controls (n = 690), n (%)	P‡	Cases (n = 658), n (%)	Controls (n = 841), n (%)	P‡
TGFBR1 genotype						
*9A/*9A	515 (84.3)	612 (88.7)	0.03	—	—	
*9A/*6A	92 (15.1)	77 (11.2)		—	—	
*6A/*6A	4 (0.6)	1 (0.1)		—	—	
TGFB1 genotype						
TT	—	—		200 (30.4)	240 (28.5)	0.23
TC	—	—		339 (51.5)	419 (49.9)	
CC	—	—		119 (18.1)	182 (21.6)	
Age (y)§						
20-40	89 (14.6)	394 (57.1)	<0.01	97 (14.7)	534 (63.5)	<0.01
41-50	166 (27.2)	82 (11.9)		181 (27.5)	84 (10.0)	
51-60	168 (27.5)	110 (15.9)		178 (27.1)	112 (13.3)	
61-70	120 (19.6)	69 (10.0)		127 (19.3)	75 (8.9)	
71+	68 (11.1)	35 (5.1)		75 (11.4)	36 (4.3)	
Mean (SD)§	54.0 (12.7)	55.3 (11.2)		53.9 (12.9)	55.4 (11.1)	
Race						
White	512 (83.8)	541 (78.4)	<0.01	544 (82.7)	649 (77.2)	<0.01
Black	44 (7.2)	43 (6.2)		53 (8.1)	51 (6.1)	
Hispanic	25 (4.1)	80 (11.6)		27 (4.1)	110 (13.1)	
Asian	18 (3.0)	22 (3.2)		20 (3.0)	26 (3.1)	
Unknown	12 (1.9)	4 (0.6)		14 (2.1)	5 (0.5)	

*The exact age was not known for 360 controls in the lowest age category (20-40 years).
†The exact age was not known for 500 controls in the lowest age category (20-40 years).
‡P for χ^2 or Fisher's exact test (comparing proportions).
§Average age for controls was calculated based on those with exact age available.

Kaklamani et al., *Cancer Res* 2005, 65:3454-3461

Table 2. Adjusted ORs of breast cancer by *TGFBR1*, *TGFB1* genotypes, and TGF-β predicted signaling status

Gene/genotype	*n* (cases/controls)	OR (95% CI) for breast cancer risk*	OR (95% CI) for breast cancer risk†
TGFBR1			
Dominant model			
9A/9A	515/612	1.00	1.00
9A/6A or 6A/6A	96/78	1.46 (1.06-2.02)‡	1.50 (1.07-2.11)‡
Additive model			
9A/9A	515/612	1.00	1.00
9A/6A	92/77	1.42 (1.03-1.96)‡	1.46 (1.04-2.06)‡
6A/6A	4/1	4.75 (0.53-42.66)	4.40 (0.48-40.52)
Recessive model			
9A/9A or 9A/6A	607/689	1.00	1.00
6A/6A	4/1	4.54 (0.51-40.73)	4.19 (0.46-38.48)
TGFB1			
Dominant model			
TT	200/240	1.00	1.00
TC/CC	458/601	0.91 (0.73-1.14)	0.98 (0.77-1.25)
Additive model			
TT	200/240	1.00	1.00
TC	339/419	0.97 (0.78-1.23)	1.02 (0.79-1.32)
CC	119/182	0.79 (0.58-1.06)	0.89 (0.63-1.21)
Recessive model			
TC or TT	539/659	1.00	1.00
CC	119/182	0.80 (0.62-1.03)	0.86 (0.65-1.14)
TGF-β predicted signaling status			
High signalers			
CC/9A9A	92/148	1.00	1.00
Intermediate signalers			
TT/9A9A, CC/9A6A, CC/6A6A, or TC/9A9A	438/475	1.48 (1.11-1.98)‡	1.27 (0.93-1.74)
Low signalers			
TT/6A6A, TT/9A6A, TC/9A6A, or TC/6A6A	78/67	1.87 (1.23-2.84)‡	1.69 (1.08-2.66)‡
P for trend		0.02‡	0.02‡

*Crude ORs.
†ORs were adjusted for ethnic groups and age as categorical variables.
‡$P < 0.05$.

Kaklamani et al., *Cancer Res* 2005, 65:3454-3461

Table 3. Adjusted ORs of breast cancer by age groups (>50 or ≤50 years)

Gene/age groups	Genotypes	*n* (cases/controls)	OR (95% CI)*	*P* for testing multiplicative interaction
TGFBR1				
Age ≤50 y	9A/9A	217/417	1.00	0.09
	9A/6A or 6A/6A	38/59	1.18 (0.75-1.84)	
Age >50 y	9A/9A	298/195	1.00	
	9A/6A or 6A/6A	58/19	2.20 (1.25-3.87)†	
TGFB1				
Age ≤50 y	TT or TC	223/477	1.00	0.99
	CC	55/141	0.85 (0.57-1.29)	
Age >50 y	TT or TC	316/182	1.00	
	CC	64/41	0.87 (0.56-1.35)	
Joint status of *TGFBR1* and *TGFB1*‡				
Age ≤50 y	High signalers	44/112	1.00	0.65
	Intermediate signalers	177/314	1.33 (0.84-2.10)	
	Low signalers	32/50	1.49 (0.77-2.87)	
	P for trend		0.19	
Age >50 y	High signalers	48/36	1.00	
	Intermediate signalers	261/161	1.23 (0.76-1.98)	
	Low signalers	46/17	2.05 (1.01-4.16)†	
	P for trend		0.06	

*ORs were adjusted for ethnic groups and age within age strata.

†$P < 0.05$.

‡Low signalers were those with TT/6A6A, TT/9A6A, TC/9A6A, or TC/6A6A; intermediate signalers were those with TT/9A9A, CC/9A6A, CC/6A6A, or TC/9A9A; and high signalers were those with CC/9A9A.

Kaklamani et al., *Cancer Res* 2005, 65:3454-3461

Association of TGF-β signaling pathway variants with breast cancer

Funded Breast CFR project

Specific Aim 1: To assess the association between carrier status of the *TGFBR1**6A allele and breast cancer risk through a discordant sibling case control association study, which will use all sibling pairs available in the Registry.

Specific Aim 2: To assess the association between the other functionally relevant variant of the TGF-β signaling pathway, *TGFB1* T29C and breast cancer risk.

Specific Aim 3: To assess the combined effects of *TGFBR1* and *TGFB1* variants that affect TGF-β signaling on breast cancer risk.

Association of TGF-β signaling pathway variants with breast cancer

Funded Breast CFR project

Secondary Aim: In secondary analyses, we will assess whether the strength of the associations of the *TGFBR1* and *TGFB1* variants with breast cancer risk in families differ according to tumor stage at diagnosis and tumor estrogen and progesterone (ER/PR) status.

We will also assess whether the associations of the *TGFBR1* and *TGFB1* variants with breast cancer risk are modified by menopausal status.

*TGFBR1**6A in Hereditary Nonpolyposis Colon Cancer

TGFBR16A* is emerging as a high frequency candidate cancer susceptibility allele.

One of every seven healty individual is *TGFBR1*6A* heterozygote and one in 200 is *TGFBR1*6A* homozygote.

Hypothesis:

*TGFBR1*6A* accounts for a proportion of MMR-mutation negative HNPCC cases?

Table 1. Demographics and Clinical Status of HNPCC Patients Meeting the Amsterdam Criteria

Characteristic	No. of Patients	%
Country of origin of index patients		
Denmark	4	1.9
Netherlands	55	26.4
Germany	48	23.1
Ireland	8	3.9
United States	61	29.3
Spain	32	15.4
MMR gene mutation status of index patients		
Positive	144	69.2
MLH1	63	30.3
MSH2	74	35.6
MSH6	7	3.3
Negative	64	30.8
Criterion met by family		
Amsterdam I	183	88.0
Amsterdam II	25	12.0
Gender of index patients		
Female	98	47.1
Male	110	52.9

Abbreviations: HNPCC, hereditary nonpolyposis colorectal cancer; MMR, mismatch repair.

***J Clin Onc* 2005, 23:3074-3078**

Table 2. *TGFBR1* Exon 1 Genotypes by MMR Gene Mutation Status

MMR Status	*9A/*9A	*9A/*6A	*6A/*6A	*6A Allelic Frequency
MMR positive (n = 144)	115	28	1	0.104
MMR negative (n = 64)	43	17	4*	0.195†

Abbreviations: MMR, mismatch repair; *9A, *TGFBR1*; *6A, *TGFBR1**6A.
**P* = 0.032 (Fisher's exact test, two sided).
†*P* = 0.011 (χ^2 test of independence).

J Clin Onc 2005, 23:3074-3078

Is *TGFBR1**6A associated with MSI status?

Table 3. *TGFBR1* Exon 1 Genotypes by Tumor MSI and Germline MMR Gene Mutation Status

	MSI-H Tumors (n = 75)				MSI-L/MSS Tumors (n = 20)			
MMR Status	*9A/*9A	*9A/*6A	*6A/*6A	*6A Allelic Frequency	*9A/*9A	*9A/*6A	*6A/*6A	*6A Allelic Frequency
MMR positive (n = 60)	45	13	1	0.127	1	0	0	0
MMR negative (n = 35)	11	4	1	0.188	12	6	1	0.211

Abbreviations: MSI, microsatellite instability; MMR, mismatch repair; MSI-H, high microsatellite instability; MSI-L, low microsatellite instability; MSS, microsatellite stable; *9A, *TGFBR1*; *6A, *TGFBR1**6A.

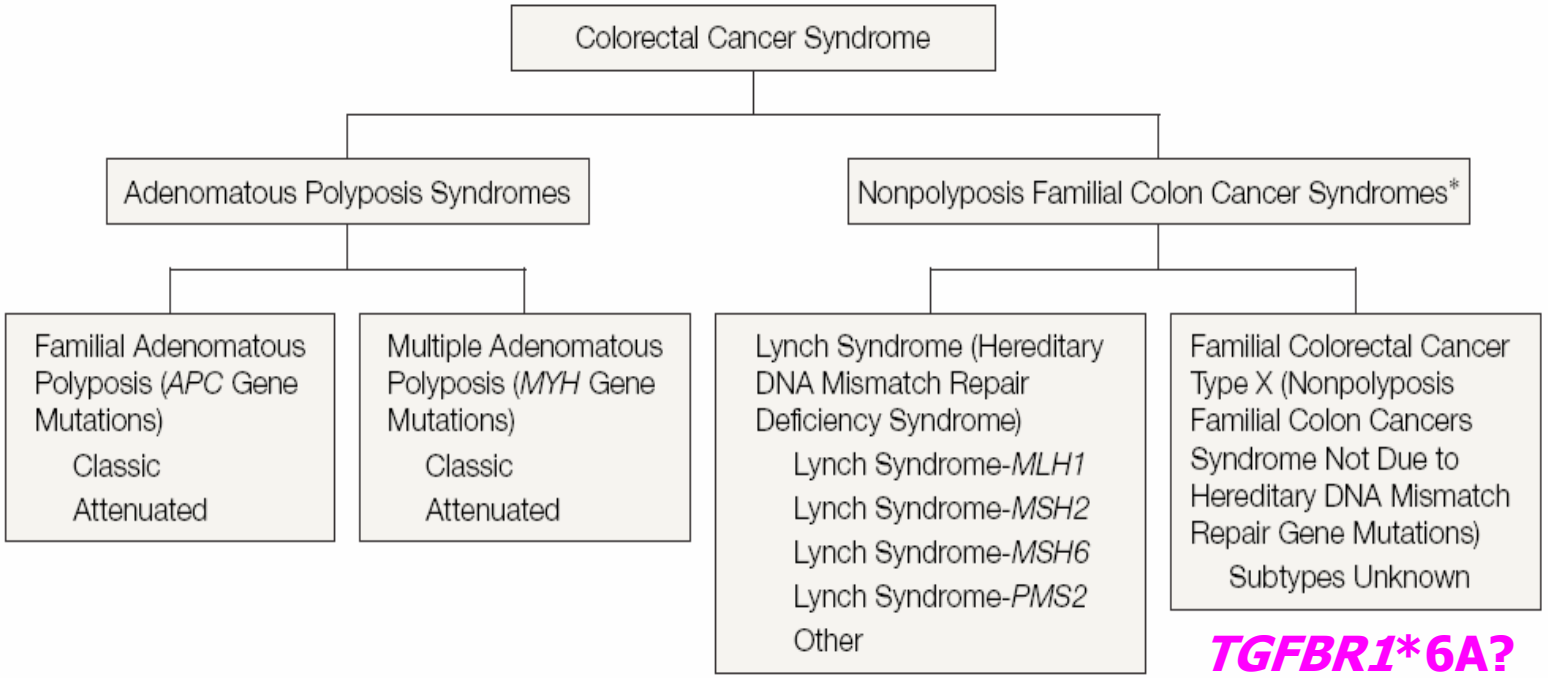
Bian et al., *J Clin Onc* 2005, 23:3074-3078

Adjusted Odds Ratios for the Associations between MMR mutation Status and *TGFBR1* Genotype

TGFBR1 Genotype	MMR mutation status (N=208)	
	N (positive/ negative)	CRUDE ORs for MMR mutation-negative (95% CI)[1]
Dominant model		
9A/9A	115/43	1.00
9A/6A or 6A/6A	29/21	1.94 (1.00-3.75)
Additive model		
9A/9A	115/43	1.00
9A/6A	28/17	1.62 (0.81-3.26)
6A/6A	1/4	10.70 (1.16-98.4)*
Recessive model		
9A/9A or 9A/6A	143/60	1.00
6A/6A	1/4	9.53 (1.04-87.1)*

[1] ORs were adjusted for age at diagnosis and gender. 9 subjects with unknown age or gender were excluded from the analysis.

Figure 2. Categories of Colorectal Cancer Syndromes

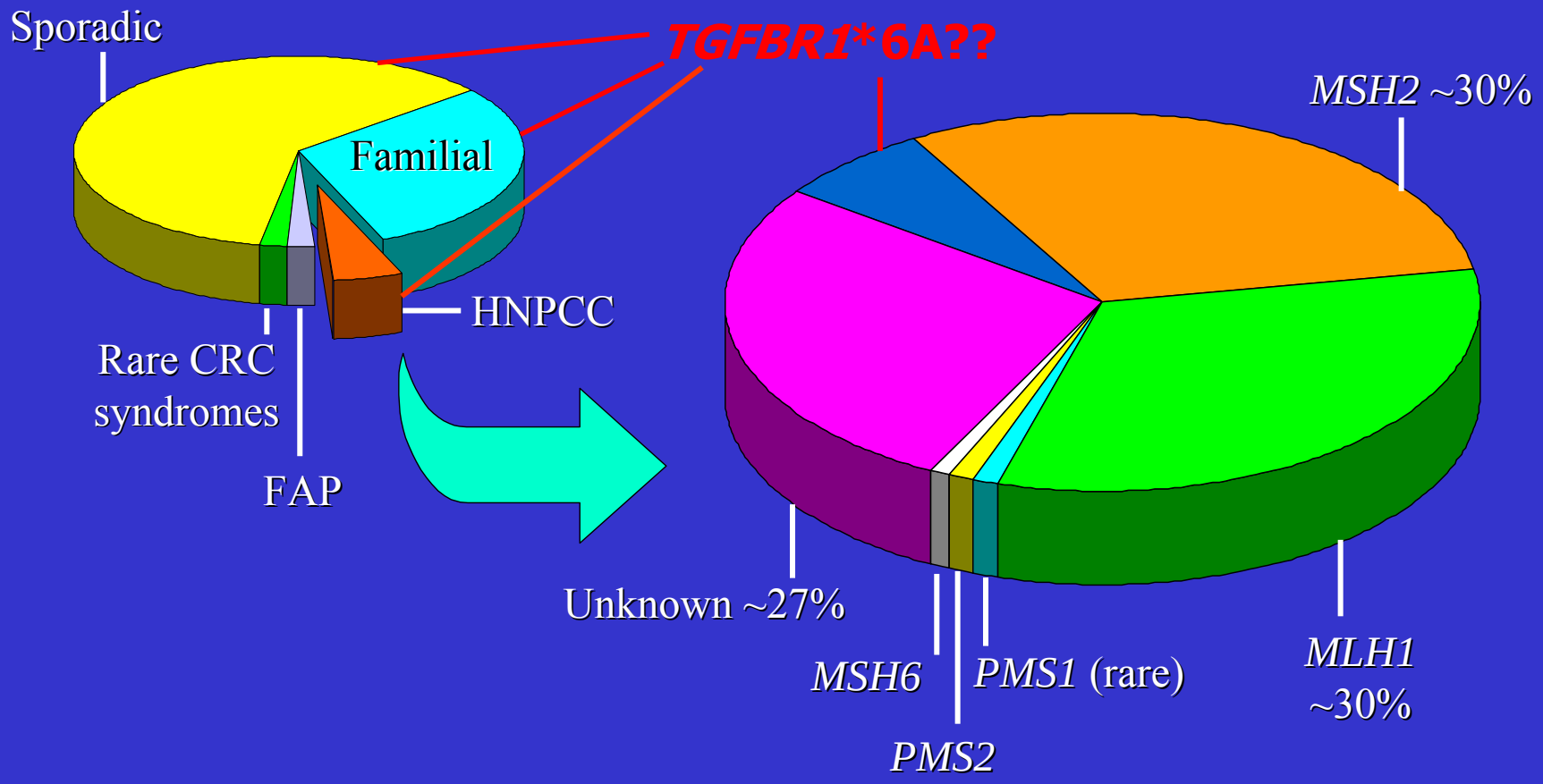


Schematic showing the 2 categories of colorectal cancer syndromes, illustrating that nonpolyposis disorders are heterogeneous but based on tumor biology can be distinguished as those having defective mismatch repair (Lynch syndrome; group A) and those with proficient mismatch repair (group B in this study, called here familial colorectal cancer type X). Diagram excludes syndromes characterized by hamartomatous/hyperplastic polyposis.

*Defined by any number of pedigree and/or laboratory criteria, including but not limited to the Amsterdam criteria. Hereditary nonpolyposis colon cancer syndrome is the term that has traditionally been used in this context, encompassing those entities that have emerged as distinguishable clinical entities (ie, Lynch syndrome and familial colorectal cancer type X).

Lindor et al., *JAMA* 2005, 293:1981-1985

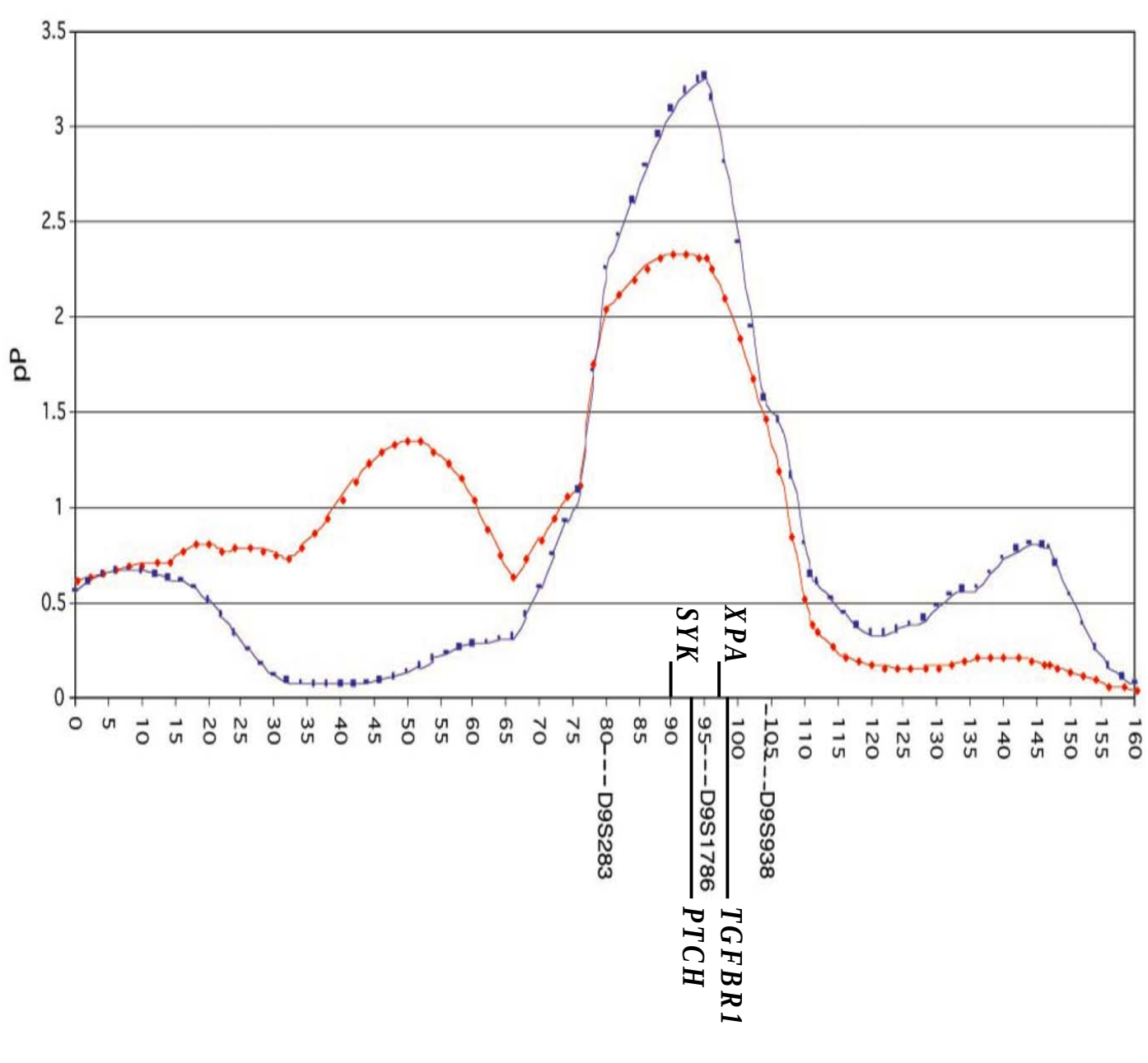
Contribution of Gene Mutations to HNPCC Families



Association of TGF-β signaling pathway variants with colorectal cancer

CFR project with fundable score

Specific Aim 1: We will assess the association between *TGFBR1**6A and colorectal cancer through a discordant sibling case control association study, which will use all sibling pairs available in the Registry. We will also perform haplotype analysis of the *TGFBR1* gene and determine the extent of the association between disease and chromosomal region 9q22.2-9q31.2. We will genotype a minimum of 4,208 full sibling case-control pairs.



Linkage of the 9q22.2-9q31.2 region to familial colorectal cancer.

Chromosome 9, in cM, is depicted along the x axis. The y axis plots *pP* = (-log10[*P* value for linkage]). Red symbols depict *pP* values for linkage as determined by the Haseman-Elston method employing all affected and unaffected siblings (modified from Wiesner et al, *PNAS*, 2003:12961-12965)

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Specific Aim 2: We will genotype cases and controls for the other functionally relevant variant of the TGF-β signaling pathway: *TGFB1* T29C, which results in higher TGFB1 circulating levels. We will also perform haplotype analysis of the *TGFB1* gene.

Specific Aim 3: We will analyze gene-gene interactions between the two well characterized *TGFBR1* and *TGFB1* polymorphisms that affect TGF-β signaling. In this aim, we will explore the relationships between the variants and colorectal cancer risk. This will allow us to determine the extent to which the overall level of TGF-β signaling, as predicted by combinations of these two variants, will be associated with colorectal cancer risk

Somatic acquisition and signaling of *TGFBR1**6A in cancer

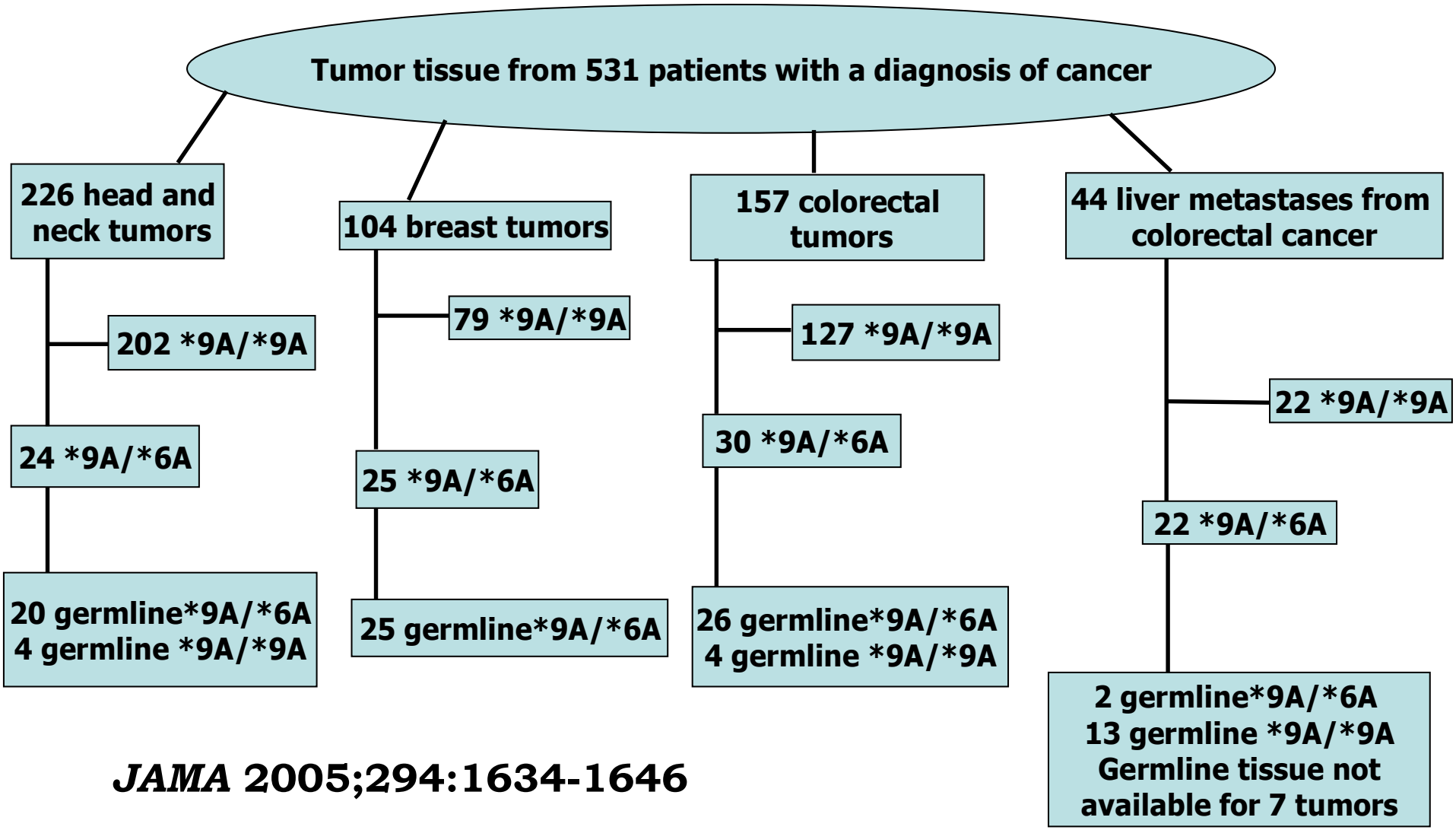
TGFBR1*6A is emerging as a common breast, colon, ovarian and prostate cancer susceptibility allele.

Hypothesis:

TGFBR1*6A may be somatically acquired during cancer development.

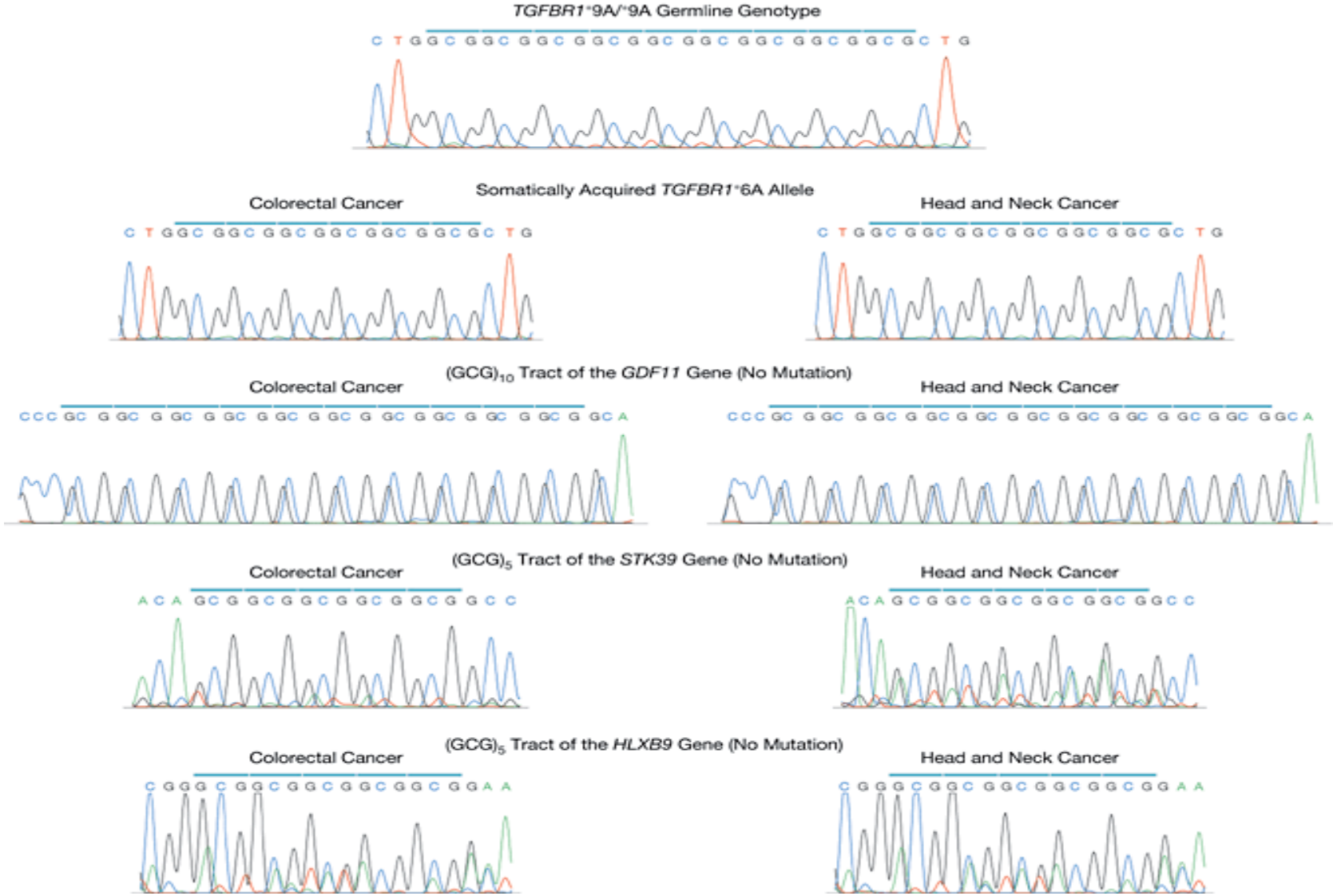
The impact of *TGFBR1**6A on TGF-β signaling in cancer cells may be different from its effects on normal epithelial cells

Flow Diagram of *TGFBR1* Exon 1 Genotyping Studies



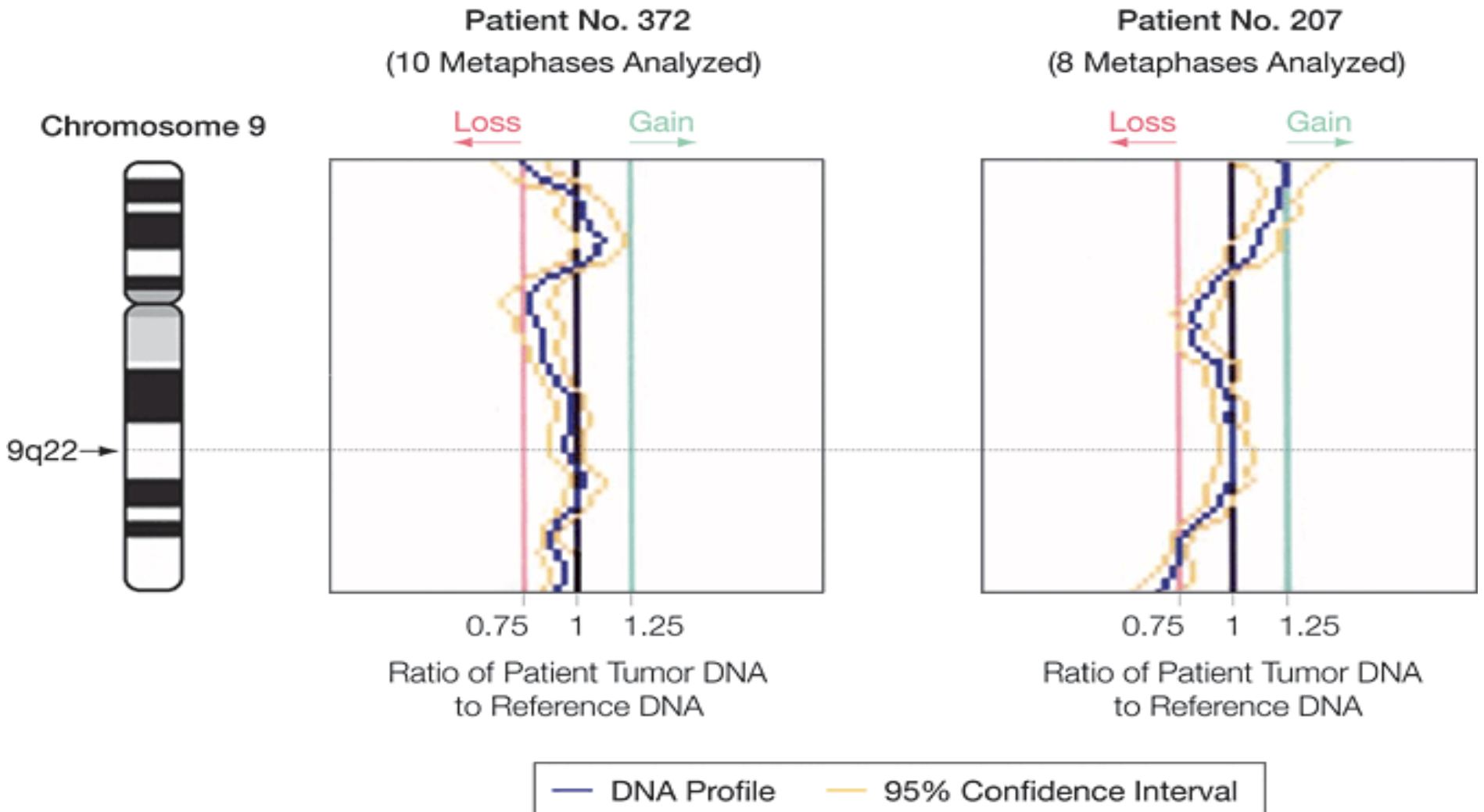
JAMA 2005;294:1634-1646

*TGFBR1**6A Somatic Acquisition and Mutator Phenotype



***JAMA* 2005;294:1634-1646**

*TGFBR1**6A Acquisition and 9q22 Deletion or Amplification in Patients With Head and Neck Cancer



JAMA 2005;294:1634-1646

TGFBR1 and *TGFBR1**6A

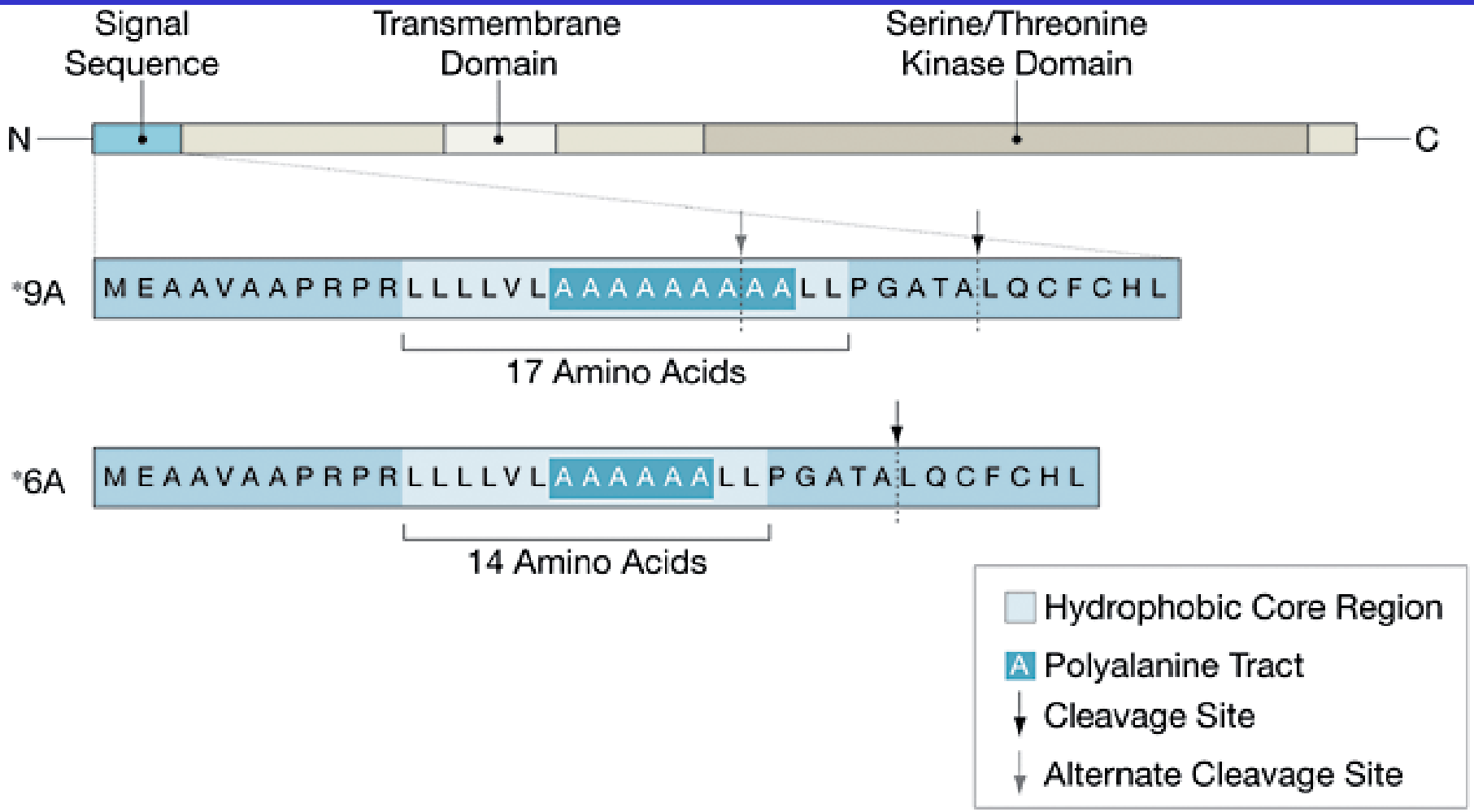
Table. Loss of Heterozygosity Assessment at 9q22 in Head and Neck and Colon Tumors With Evidence of *6A Acquisition

	Microsatellite Markers				
Patient	D9S287	D9S180	D9S1851	D9S1786	D9S176
Head and neck cancer					
48	NI	. . .	. . .	I (equal)	. . .
207	NI	I (equal)	. . .	I (equal)	I (equal)
372	. . .	. . .	. . .	I (equal)	NI
Colon cancer					
597	I (equal)	I (equal)	. . .	I (equal)	. . .

Abbreviations: I, informative marker because of heterozygosity; NI, noninformative; ellipses, not attempted.

JAMA 2005;294:1634-1646

TGFBR1 and *TGFBR1**6A



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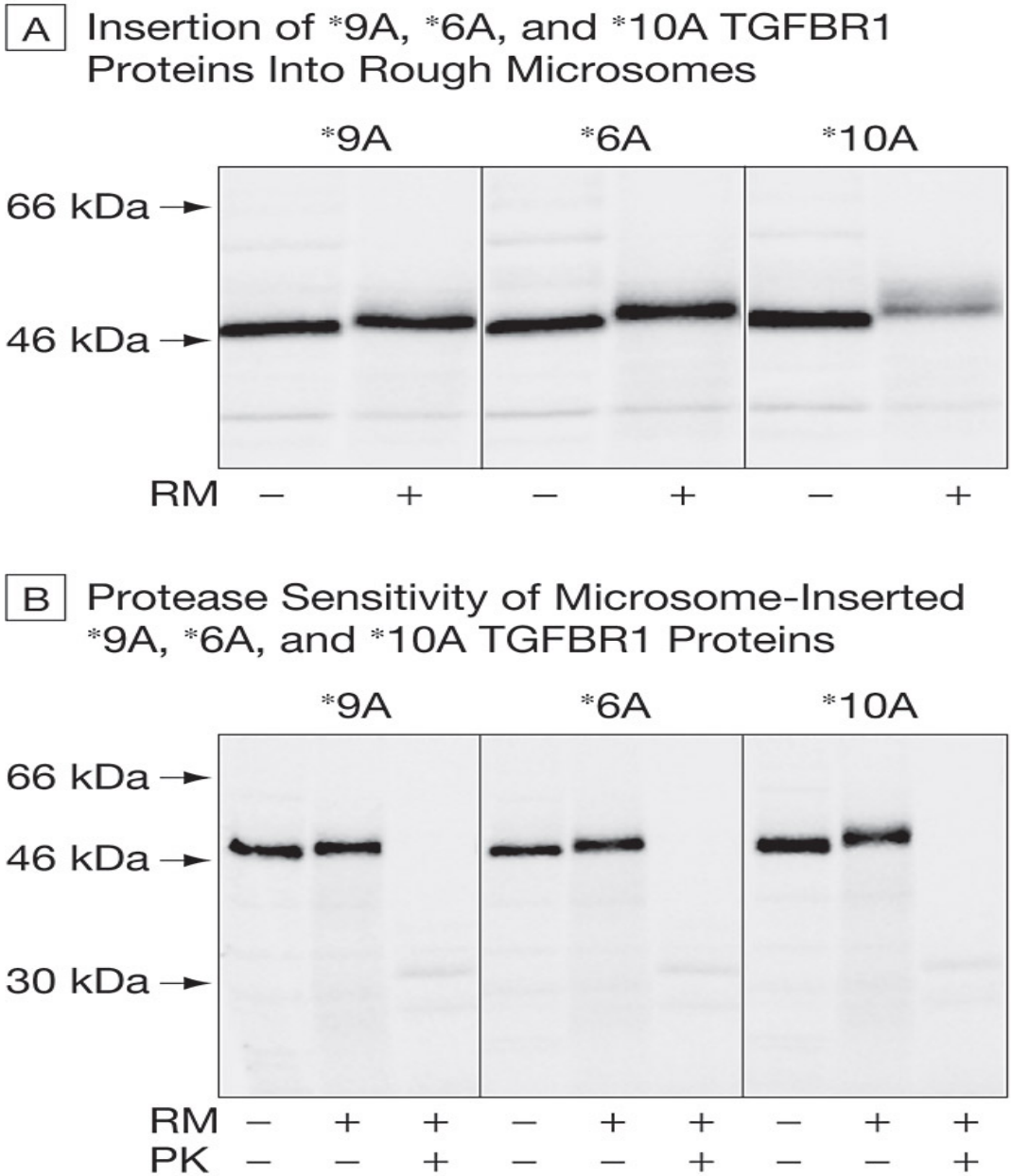


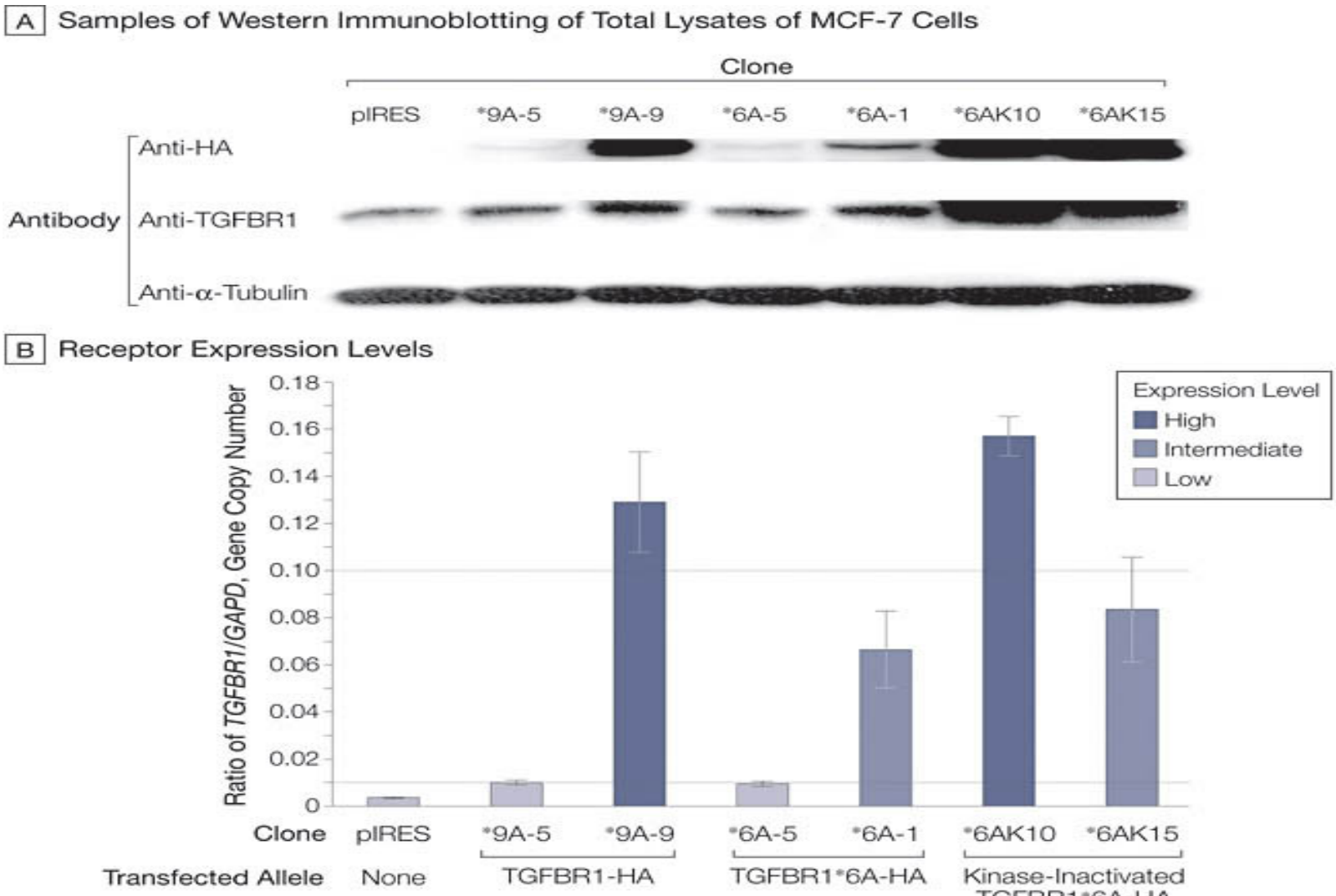
In vitro translation of pCS2-TGFBR1, pCS2-TGFBR1*6A, and pCS2-TGFBR1*10A *in vitro* in the presence of rough dog pancreas microsomes under standard conditions.

All three proteins were efficiently inserted into the microsomal membrane as evidenced by efficient glycosylation of the unique glycosylation acceptor site in the short extracellular domain of the protein (A) and protease-sensitivity of the large cytoplasmic domain in intact microsomes (B).

Thus, neither the 9 bp deletion in the *6A signal sequence nor the 3 bp insertion in the *10A signal sequence measurably affect either targeting to or translocation across the endoplasmic reticulum membrane.

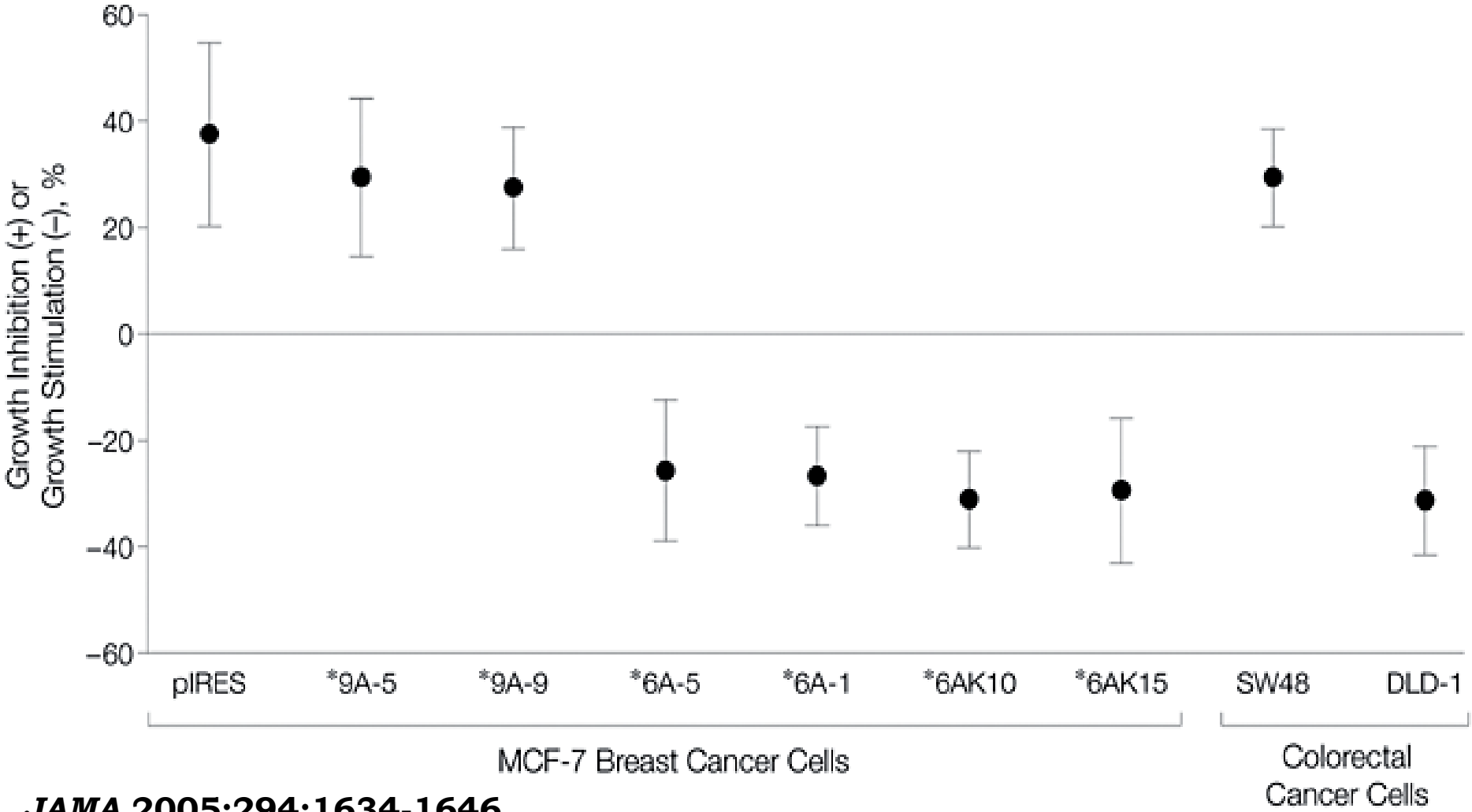
Pasche, B. et al. *JAMA* 2005;294:1634-1646

TGFBR1 Expression Levels of Stably Transfected MCF-7 Clones

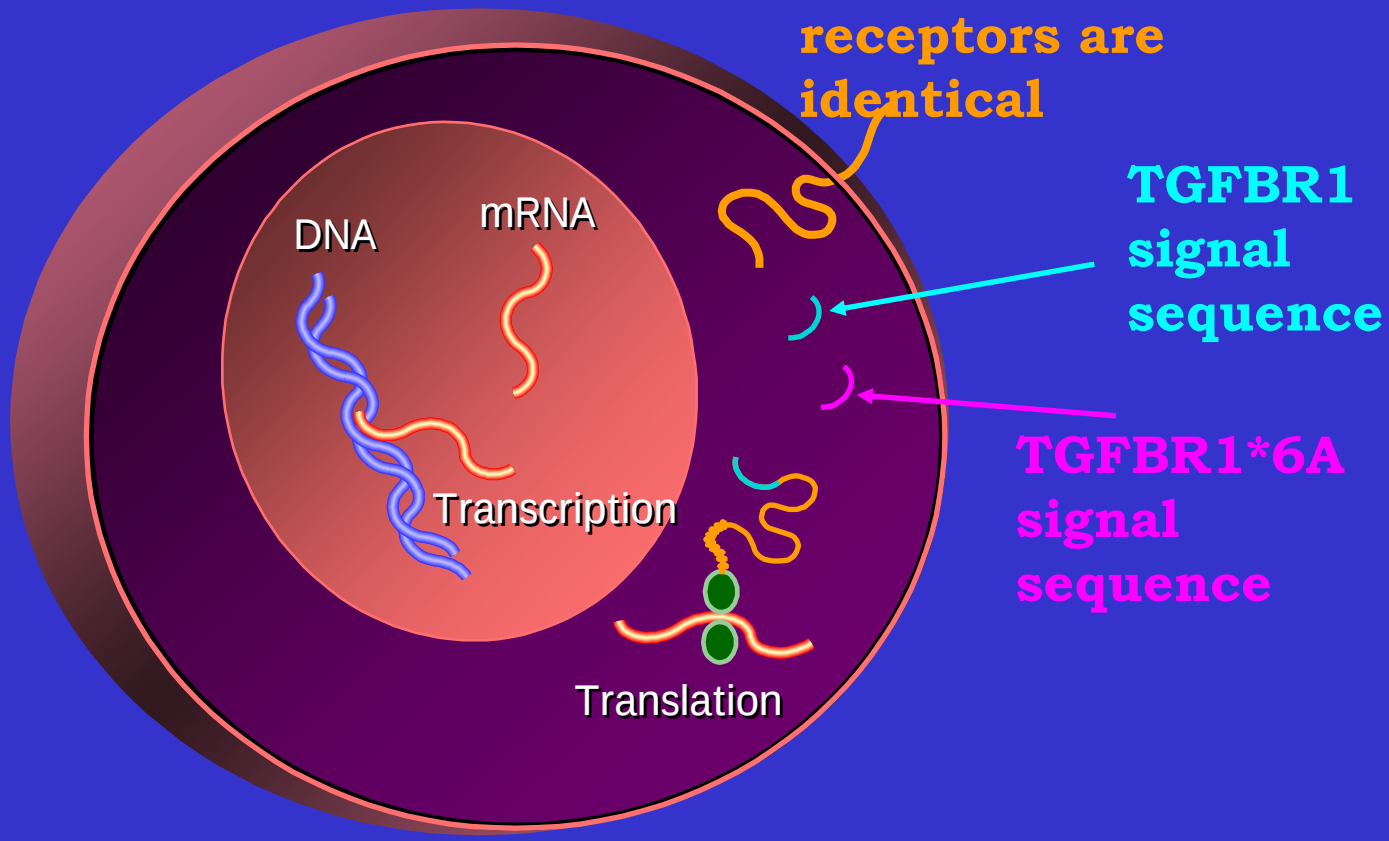


***JAMA* 2005;294:1634-1646**

TGF-β Growth Inhibition and Stimulation Assays of Stably Transfected MCF-7 Cells and SW48 (*9A/*9A) and DLD-1 (*6A/*9A) Colorectal Cancer Cell Lines

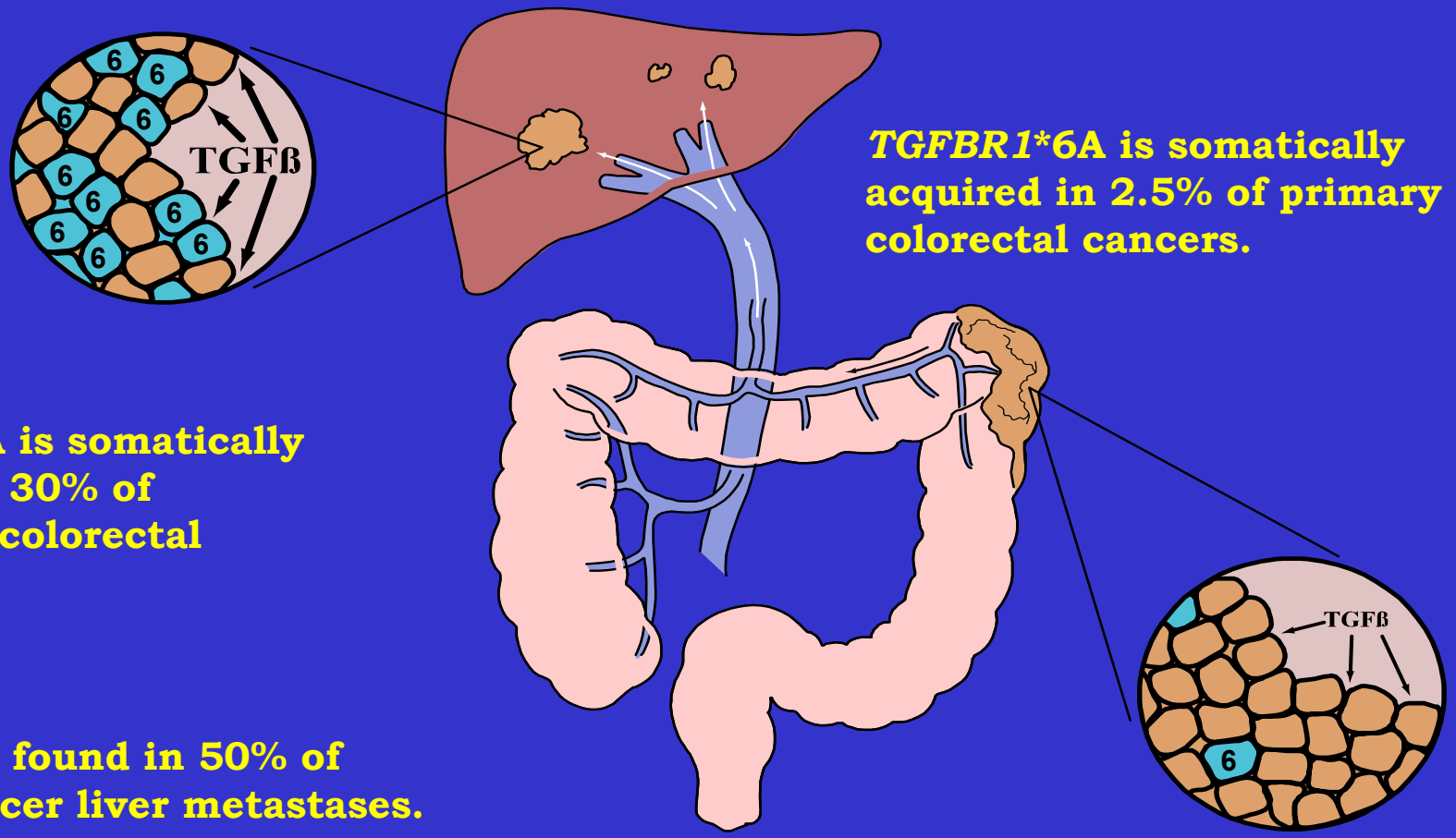


JAMA 2005;294:1634-1646



The biological actions of *TGFBR16A are likely due to its signal sequence secondary signaling effects**

*TGFBR1**6A and colorectal cancer

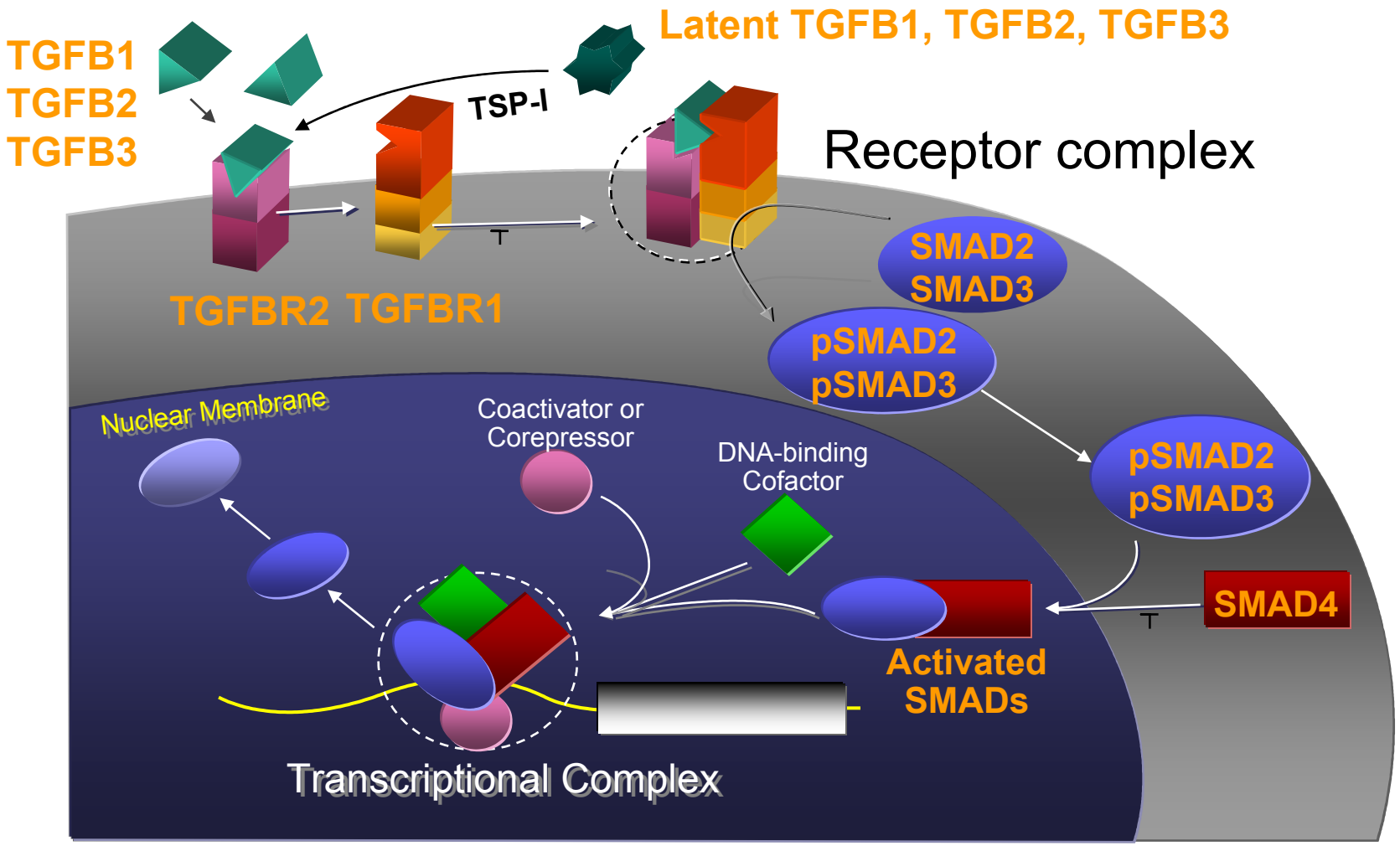


***TGFBR1**6A is somatically acquired in 2.5% of primary colorectal cancers.*

***TGFBR1**6A is somatically acquired in 30% of metastatic colorectal cancers.*

***TGFBR1**6A is found in 50% of colorectal cancer liver metastases.*

Breast cancer SPORE CFR project (Feb 1, 2006)



Comprehensive haplotype analysis of the TGF-β pathway

CONCLUSIONS

***TGFBR1**6A is emerging as a low to moderate penetrance tumor susceptibility allele. One in every two hundred healthy individual is a ***TGFBR1**6A homozygote.

Meta-analyses indicate that ***TGFBR1**6A homozygotes have a 200% increased prostate cancer risk, 169% increased breast cancer risk and 107% increased ovarian cancer risk.

A combined assessment of two well-characterized, functionally relevant variants of the TGF-β signaling pathway may predict cancer risk in a large proportion of the general population.

***TGFBR1**6A may contribute to a fraction of mismatch repair mutation-negative hereditary colorectal cancer "Familial colorectal cancer type X".

***TGFBR1**6A is somatically acquired in 30% of patients with liver metastases from colorectal cancer. ***TGFBR1**6A switches TGF-β growth inhibitory signals into growth stimulatory signals by means of its signal sequence.

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